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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,372	DAHL ET AL.	
	Examiner	Art Unit	
	CYNTHIA B. WILDER	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *172-197* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *172-197* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 8/7/2009 is acknowledged and has been entered. Claims 1-171 and 198-205 have been canceled. Claim 172 has been amended. Claims 172-197 are pending. All of the arguments have been thoroughly reviewed and considered but are deemed moot in view of the new grounds of rejections necessitated by Applicant's amendment of the claims. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

This action is made FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Previous Rejections

3. The prior art rejection under 35 USC 103(a) directed to claims 172, 174 and 195 as being unpatentable over Kurn et al in view of Dai et al is withdrawn in view of Applicant's amendment of the claims. The prior art rejection under 35 USC 103(a) directed to claims 173, 175-186, 194 and 195 as being unpatentable over Kurn et al in view of Dai et al in view of Kacian et al and further in view of Ginsberg et al is withdrawn in view of Applicant's amendment of the claims. The prior art rejection under 35 USC 103(a) directed to claims 187-193, 196 and 197 as being unpatentable over Kurn et al in view of Dai et al and Kacian et al and Ginsberg et al and further in view of Diegelman et al is withdrawn in view of Applicant's amendment to the claims.

Claim Rejections - 35 USC § 103

4. The following are new grounds of rejections necessitated by Applicant's amendments. Although the claims were previously rejected as being anticipated by the same reference, Applicant's amendments have necessitated the inclusion of new grounds of rejections in the present rejection. It is noted that, to the extend that they apply to the present rejection; Applicant's arguments are addressed following the rejection.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 172, 174, and 195 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kurn et al (20020058270, May 2002) in view of Dai et al

(Genes & Development, vol. 12, pages 2782-2790, September 1998). Regarding claims 172, Kurn et al teach a method for making a transcription product having a sequence corresponding to a target sequence in a target nucleic acid in a sample, the method comprising the steps of: (a) obtaining an RNA polymerase that can transcribe RNA using a promoter sequence, wherein said promoter is a double-stranded promoter; (b) obtaining single-stranded DNA comprising the target sequence that is present in or complementary to a sequence in the target nucleic acid in the sample; (c) operably joining to the single-stranded DNA a single-stranded polynucleotide comprising a promoter that binds the RNA polymerase, thereby obtaining a single-stranded transcription substrate; (d) obtaining nucleoside triphosphates (NTPs) that are substrates for the RNA polymerase and that are complementary to canonical nucleic acid bases; admixing the RNA polymerase, the single-stranded transcription substrate and the NTPs; (e) and (f) incubating the RNA polymerase, the single-stranded transcription substrate and the NTPs to synthesize the transcription product (0053, 0067, 0076, 0099, 0100, 0107-0112).

Regarding claim 174, Kurn et al teach wherein the single-stranded DNA comprising the target sequence is obtained using a target nucleic acid comprising: (a) DNA; (b) at least one mRNA; or (c) substantially all mRNA in a sample (0161).

Regarding claim 195, Kurn et al teach wherein at least one of the NTP comprise 2-fluoro- or 2-azido (see 0066).

Kurn et al do not expressly teach that the RNA polymerase transcribes

RNA using a single stranded promoter. However, Kurn et al teach that a propromoter template switch oligonucleotide method can be employed in the invention. Kurn teaches that in this method, both the primer and propromoter comprises a 3' portion which is complementary to the target polynucleotide; and a 5' portion which is not hybridization the target under a given set of conditions, wherein the non-hybridizable 5' portion comprises a sequence that is a single strand of a promoter for a DNA dependent RNA polymerase used in the amplification steps according to the methods of the invention (claim 176) (paragraph 0141).

Dai et al teach a RNA polymerase that is capable of transcribing an RNA using a single stranded promoter (see abstract and page 2782). Dai et al also teaches wherein the RNA polymerase transcribes hairpin promoter structures in the presence of a single stranded binding protein (see page 2782 and pages 2787-2789). Dai et al teach wherein the polymerase is N4-vRNAP (see abstract and entire reference). Dai et al also teach mutant forms of N4-vRNAP (see e.g., Tables 1 and 2).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the claimed invention to have been motivated to have utilized an RNA polymerase, such as the mutant N4 virion RNA polymerase, as taught by Dai in the method of Kurn et al, since Kurn teaches performing a transcription-based assay in the presence of a single stranded promoter (see 0141). An ordinary artisan would have been motivated to use any RNA polymerase known to possess this activity when practicing the transcription-based assay of Kurn

recognizing its suitability for the intended purposes. As noted in MPEP 2144.07, a selection of a known material based on it's suitability for the intended purpose is *prima facie* obvious in the absence of secondary consideration. Also noted in MPEP 2144.06, it is *prima facie* obvious to substitute art-recognized equivalent useful for the same purpose. In this case, the ordinary artisan could predictably expect a reasonable expectation of success using the mutant RNA polymerase of Dai et al in the method of Kurn, since the use of the RNA polymerase as taught by Dai et al does not effect, modify or hinder the function of the transcription based assay, as Kurn recognizes the usefulness of RNA polymerases which are capable of transcribing an RNA using a single stranded promoter (See Kurn 0141).

Response to Arguments

8. Applicant traverses the rejection on the grounds that neither Kurn nor Dai et al teach wherein the RNA polymerase is an N4 mini vRNAP or the Y678F mutant of the mini-vRNAP. Applicant cites paragraph 0072 as support and further states that surprisingly N4 mini vRNAP deletion mutant which comprises only about one-third of the amino acids of the wild type phage N4 vRNAP known in the art, is fully active for *in vitro* transcription.

9. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons that follow: In response Applicant arguments that the references do not teach the RNA polymerase as currently claimed, it is noted that neither Applicant's specification or claims provide a limiting definition of mini-vRNAP. The specification appears to suggest that

mini-vRNAP is a mutant form of the wild type N4-vRNAP. The claims are not limited by any specific sequence structure and thus there is nothing in the claims which would exclude any mutant form of N4-vRNAP as representing a mini N4-vRNAP. In regards to Applicant's assertion of surprising results, Applicant provides evidence to support this conclusion. According Applicant's arguments are not found persuasive.

10. Claims 173 and 175-186, 194 and 195 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kurn et al in view Dai et al as previously applied in view Kacian et al (Citation made of record in prior Office action) and further in view of Ginsberg et al (citation made of record on IDS 6/24/2006).

Regarding claim 173, Kurn et al in view of Dai et al teach a method as previously described above. Kurn et al further teach additional steps or repetition of second set of transcription steps using the sense strand of final process steps from the first transcription as the starting substrate which results in exponential amplification of the sequence of interest or second transcription product (see 0050, 0067 and 0100). Kurn et al teach wherein the method may utilize an RNA-dependent DNA polymerase such as reverse transcriptase (0142) in the formation of single stranded cDNA from a primer-RNA complex (0023 and 0024).

Kacian et al teach a method similar to that of Kurn et al for making a transcription product. Kacian et al teach the use of reverse transcriptase in method steps for synthesizing a cDNA from the initially synthesized cDNA strand (see col. 45-46, section F). MPEP 2144.04 notes, "selection of any order of

performing process steps is *prima facie* obvious in the absence of new or unexpected results".

Nonetheless, Ginsberg et al teach a method of making a transcription product having a sequence corresponding to a target sequence in a target nucleic acid sample, wherein the method comprises the additional steps of obtaining a reverse transcriptase, reverse transcribing the transcription product to obtain a first strand cDNA complementary to the transcription product and incubating the first strand cDNA product in the presence of a single stranded polynucleotide comprising a promoter that binds to an RNA polymerase, mixing and incubating the RNA polymerase, the single stranded transcription substrate and NTPs to synthesize a second transcription product (0020-0026, 0030-0036 and especially 0044). Ginsberg et al teach that the method is highly efficient with improved sensitivity (see 0023).

Therefore, in view of the foregoing, it would be predictable to one of ordinary skill in the art at the time of the claimed invention that multiple products as produced by the transcription method of Kurn et al in view of Dai et al can be synthesized efficiently to produce additional products corresponding to the target sequence as taught by Kacian et al and Ginsberg et al with a reasonable expectation of success.

Regarding claim 175, Kacian et al teach wherein the single-stranded transcription substrate of step (c) is obtained by primer extension of the single-stranded DNA of step (b) using a promoter splice template oligo annealed to the 3'-end of the single-stranded DNA as a template, said splice template oligo

comprising: (a) a 5'-end portion that is complementary to a desired sequence to be added to the 3'-end of the first-strand cDNA; and (b) a 3'-end portion that is complementary to the 3'-end of the first-strand cDNA, wherein the 3'-terminus is blocked so it cannot be primer extended using a DNA polymerase (col. 4, 7 and col. 14)..

Regarding claim 176, Kacian et al teach wherein the 5'-end portion of said splice template oligo is complementary to part of or all of a sense or an anti-sense promoter sequence for an RNA polymerase that can bind a single-stranded promoter (col. 7 and col. 13).

Regarding claim 177, Kacian et al teach wherein the single-stranded DNA is obtained by reverse transcription of a transcription product (col. 8, lines 40-48 and col. 45, section F).

Regarding claims 178-186, Kacian et al teach wherein the method comprise the sub-steps of: (al) obtaining a primer for synthesis of a first-strand cDNA, the primer comprising a sequence complementary to the sequence at the 3'-end of the target sequence to be transcribed; (bl) annealing the primer to the target nucleic acid; (cl) primer-extending the primer annealed to the target nucleic acid with a DNA polymerase to obtain a linear first-strand cDNA comprising a sequence complementary to the target sequence; (dl) obtaining a promoter splice template oligo comprising: (i) a 3'-end that is sufficiently homologous to the 3'-end of the linear first-strand cDNA, including the tail if present, to hybridize therewith, and that is blocked so that it cannot itself be primer-extended by a DNA polymerase; and (ii) a 5'-portion that exhibits a sequence that is

complementary to a transcription promoter for an RNA polymerase that can synthesize RNA using a single-stranded transcription substrate; (el) annealing the promoter splice template oligo to the linear first-strand cDNA including the tail if present; (fl) primer-extending the linear first-strand cDNA including the tail, if present, with a DNA polymerase to obtain a promoter-containing linear first-strand cDNA that has a 3'-portion that is complementary to the portion of the promoter splice template oligo that is not hybridizable to the first-strand cDNA including the tail, if present; and (gl) removing or dissociating the promoter splice template oligo from the promoter-containing linear first-strand cDNA to obtain the single-stranded transcription substrate. Kacian et al additionally teach wherein the method comprises (a2) obtaining a blocking oligo, the blocking oligo comprising a sequence that anneals to the target nucleic acid so as to delimit the 3'-end of a primer extension product of the primer using the target nucleic acid as a template, wherein the blocking oligo is not displaced by the primer extension product, and wherein the blocking oligo is not itself capable of being primer-extended by a DNA polymerase; and (b2) annealing the blocking oligo, together with the primer, to the target nucleic acid in step (b1) prior to primer-extending the primer in step (c1) (cols. 4-8, 21 and 45). Kacian et al teach removal of the original target using RNAse H (col. 31, lines 27-30).

In regards to the limitation concerning the selection of the primer for synthesis of a linear first strand cDNA, Kurn et al teaches wherein a random primer may be used for synthesis of a liner cDNA strand (paragraphs 0072 and 0186).

In regards to the limitation wherein a tail is added to the first strand cDNA, Ginsberg et al teach this limitation (Figure 9). In regards to the order of method steps as recited in the rejected claims, it is noted that MPEP 2144.04 notes "selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results".

Regarding claim 194, Ginsberg et al teach wherein the target has a tail sequence comprising at least two nucleotides (see figure 9).

11. Claims 187-193, 196 and 197 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kurn et al in view of Dai et al and Kacian et al and Ginsberg et al as previously applied above and further in view of Diegelman et al (Nucleic Acids Research, vol. 26, no. 13, pages 3235-3241, 1998). Regarding claims 187-193, 196 and 197, Kurn et al in view of Dai et al in view of Kacian in view of Ginsberg et al teach a method for making a transcription product having a sequence corresponding to a target sequence as previously applied above. The references however do not teach the steps of circularizing the antisense promoter with a ligase and obtaining a circular single stranded transcription substrate. Likewise, the references do not teach the use of a ligation splint or wherein the transcription product comprises a hairpin RNA. However, Kurn et al do teach the formation of hairpin loop via self-ligation (see 0071) and Dai et al teach the use of an RNA polymerase that transcribes hairpin promoter structures (page 2782 and pages 2787-2789).

Diegelman et al teach a method for the in vitro synthesis of circular RNA

and formation of hairpin transcription products. Diegelman et al teach wherein ligation conditions comprises using a ligation splint, addition of a ligase in the presence of a T7 RNA polymerase (see "Material and Methods, page 3225, col. 2 to page 3226 col. 1). Diegelman et al teach this method can be successful in producing amplified amounts of both circular and linear hairpin (see 3239, col. 2). Diegelman et al teach that this rolling circle strategy may be useful for the generation of certain biological relevant RNAs (page 3240, col. 2).

Therefore, in view of foregoing, it would be obvious to one of ordinary skill in the art at the time of the claimed invention that a rolling circle strategy can successfully result in the making of a transcription product as suggested by Diegelman et al with a reasonable expectation of success. The combination of Kurn et al in view of Dai et al in view of Kacian et al in view of Ginsberg et al and further in view of Diegelman et al is *prima facie* in the absence of secondary consideration.

Response to Arguments

11. Applicant traverses the rejection on the grounds that none of the references teaches a sense promoter primer to make a transcription substrate. The Examiner respectfully disagrees because Kurn teaches primers which may hybridize to the sense strand of a DNA strand (0015 and 0016). Therefore, this argument is not found persuasive.

Conclusion

12. No claims are allowed. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION**

IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GARY BENZION/
Supervisory Patent Examiner, Art Unit 1637